

Lung function, airway responsiveness, and respiratory symptoms before and after bronchiolitis

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Abstract

Acute viral respiratory illness during infancy has been implicated as a precursor for subsequent lower respiratory morbidity in childhood. A prospective, longitudinal study of respiratory function, airway responsiveness, and lower respiratory illness during early childhood was performed in a cohort of 253 healthy infants to characterise those who experienced bronchiolitis. Seventeen infants (7% of the cohort), were given a diagnosis of bronchiolitis during the first two years of life with two (1%) requiring hospital admission. Seventy one per cent of those infants with bronchiolitis had a family history of atopy, 53% of asthma, and 29% had a mother who smoked cigarettes. These family history characteristics in this group with bronchiolitis were not different from the rest of the cohort. There were also no differences in the number of older siblings, the number breast fed, the duration of breast feeding, or socioeconomic status of the families between those that did and did not get bronchiolitis. Respiratory function was assessed at 1, 6, and 12 months of age. Maximum flow at functional residual capacity ($\dot{V}_{\max\text{FRC}}$) was measured using the rapid thoracic compression technique. Resistance (Rrs) and size corrected compliance (Crs/kg) were obtained from a single brief occlusion at end inspiration. Airway responsiveness was assessed by histamine inhalation challenge and the provocation concentration of histamine resulting in a 40% fall on $\dot{V}_{\max\text{FRC}}$ from baseline (PC_{40}) was determined. Respiratory measurements were ranked into terciles to assess the distribution of infants who developed bronchiolitis through the cohort. At the age of 5 weeks, a significant trend was observed for infants who subsequently developed bronchiolitis during the first year of life to have baseline $\dot{V}_{\max\text{FRC}}$ values in the lowest tercile (odds ratio 3.16, 95% confidence interval 0.87 to 11.6). Rrs, Crs/kg, and PC_{40} were not different at any age between the bronchiolitics and the cohort. Cough and wheeze were noted to be frequent before the episode of bronchiolitis. This study has demonstrated that infants who develop bronchiolitis have evidence of pre-existing reduced respiratory function and lower respiratory symptoms. It is proposed that bronchiolitis, although

potentially contributory, is not usually causative of subsequent lower respiratory morbidity.

(Arch Dis Child 1995; 72: 16-24)

Keywords: bronchiolitis, respiratory function, histamine inhalation challenge, lower respiratory symptoms.

Acute viral respiratory infection during infancy is common, with symptoms ranging from those that are mild and restricted to the upper airway to those that indicate involvement of the lower respiratory system, and in some, the development of features characteristic of the clinical entity described as bronchiolitis. Bronchiolitis has received particular attention as it has been suggested that an episode of bronchiolitis in the first two years of life causes subsequent lower respiratory morbidity or that bronchiolitis identifies those infants predisposed to develop asthma.¹ Studies have documented abnormal pulmonary function, increased airway responsiveness, increased lower respiratory symptoms, and impaired oxygenation in children with a history of bronchiolitis.²⁻¹⁸ Some have documented an increased incidence of atopy and raised concentrations of IgE,^{2 5 7-12 14-19} while others have not.^{11 20}

Environmental factors, such as passive tobacco smoke exposure, have also been suggested to predispose an infant exposed to respiratory syncytial virus for increased lower respiratory disease, particularly bronchiolitis.²¹ Breast feeding, the number of older siblings, and socioeconomic status have also been implicated to influence whether an infant will develop bronchiolitis,^{3 4 8} while others have not identified such associations.^{10-13 15 17 20 22}

The ability to test each of these hypotheses is reliant on documenting those factors believed to be important in the development of and potentially resulting from bronchiolitis before and after infection. The majority of studies in the literature are based on infants hospitalised for bronchiolitis,^{5 7 8 10-13 17 19 20} who are then followed up prospectively from the time of hospitalisation.^{9 14-16 23} These study populations represent the most severe end of the disease spectrum. Children have been studied many years after bronchiolitis so that it is not possible to differentiate between effects due to the bronchiolitis or ongoing environmental insults encountered during the intervening period from initial infection to assessment.

During our longitudinal study of genetic and environmental influences on lung

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Accepted 13 September
1994

function, airway responsiveness, and lower respiratory illness in a cohort of healthy infants, 7% were diagnosed as having bronchiolitis during the first two years of life. We assessed the natural history of the cohort throughout the first two years of life to test the hypothesis that pre-existing lower respiratory function abnormalities in early life predispose infants to bronchiolitis.

Subjects and methods

SUBJECTS

The infants in this study were part of a prospective, longitudinal study of lung function, airway responsiveness, and lower respiratory illness during the first two years of life. The inclusion criteria were full term gestation, an absence of perinatal problems, and no major congenital anomalies.

The families of all the infants were recruited at the antenatal clinic at Osborne Park Hospital, Perth, Western Australia. Total cohort recruitment spanned May 1987–December 1991 during which time 1011 mothers were interviewed and 253 (25%) consented to participation. The recruitment process has been documented previously.²⁴ In brief: the mother was interviewed during a routine antenatal visit and given an information sheet detailing involvement over the study period. Telephone contact was made subsequent to the interview to determine willingness to participate. The study was performed with the approval of the medical ethics committees of Princess Margaret Hospital for Children and the University of Western Australia.

Two hundred and forty six infants (135 boys) were initially studied at a mean age of 5 weeks (range 2–10). At the initial lung function assessment, no infant had previously had a lower respiratory illness or any clinically important non-respiratory illness. Repeat measurements were made at 6 and 12 months of age and at each assessment all the infants were well, with no upper or lower respiratory tract infection in the preceding three weeks.

FAMILY HISTORY

The family history of asthma, atopy in primary relatives (mother, father, siblings) and/or secondary relatives (grandparents, aunts, uncles), and parental smoking habits during the pregnancy, the number of older siblings, and socioeconomic status (based on paternal occupation) were obtained using a modified American Thoracic Society questionnaire²⁵ administered by one of two investigators (SY, JA) at the first infant assessment.

INFANT LUNG FUNCTION

Respiratory function was assessed at 1, 6, and 12 months of age using the rapid thoracic compression technique.²⁶ This technique as used in our laboratory has been described previously.²⁷ In summary: an inflatable jacket was wrapped around the ribcage and abdomen of the infant. The jacket was rapidly inflated at

end inspiration and flow measured at function residual capacity from the resulting partial expiratory flow-volume curve. The jacket pressure was gradually increased (10–80 cm H₂O) over a series of forced expirations until no further increase in flow occurred with an increase in pressure and it was assumed maximum flow at functional residual capacity ($\dot{V}_{\max}^{\text{FRC}}$) was reached.

Infants were studied while asleep after receiving chloral hydrate (60–80 mg/kg). Baseline $\dot{V}_{\max}^{\text{FRC}}$ was established after the administration of nebulised normal saline with an Airlife nebuliser (American Pharmaseal) run at 6 l/min from a compressed air source. The mean of five forced expirations was used as the baseline $\dot{V}_{\max}^{\text{FRC}}$ reference value.

Compliance (Crs) and resistance (Rrs) of the total respiratory system were measured from a passive flow-volume slope after a single brief occlusion at end inspiration inducing the Hering-Breuer reflux.²⁸ Crs was size corrected by dividing by the infant's weight.

The pattern of tidal breathing was assessed by measuring the ratio of time to maximum expiratory flow/total expiratory flow ($T_{\text{me}}/T_{\text{e}}$)²⁹ from a tidal flow-volume loop. $T_{\text{me}}/T_{\text{e}}$ was averaged from 10 consecutive tidal breaths recorded at baseline.

INFANT AIRWAY RESPONSIVENESS

The histamine inhalation challenge was carried out using doubling concentrations of nebulised histamine from 0.125 g/l to a maximum concentration of 8.0 g/l, as previously described.²⁷ A new concentration was delivered every five minutes and respiratory function assessed after each concentration, with a minimum of five forced expirations being performed. The challenge ceased when a response to histamine was recorded or the maximum concentration reached. A response was defined as a fall in $\dot{V}_{\max}^{\text{FRC}}$ of at least 40% from baseline. The provocative concentration producing a 40% fall in $\dot{V}_{\max}^{\text{FRC}}$ (PC_{40}) was derived by linear interpolation from the plot of log histamine concentration against per cent fall in $\dot{V}_{\max}^{\text{FRC}}$ from baseline.

ARTERIAL OXYGEN SATURATION MONITORING

Arterial oxygen saturation (SaO_2) was monitored throughout the study using a Nellcor N-200 E pulse oximeter (Nellcor) in beat to beat mode. The SaO_2 level after saline nebulisation was taken as the baseline reference value. For each nebulisation, SaO_2 was recorded immediately before and after administration. SaO_2 was monitored throughout forced partial expiratory manoeuvres and no effect of forced expiration on SaO_2 was observed. Supplemental oxygen was administered if SaO_2 fell below 90%.

INFANT SKIN ALLERGEN ASSESSMENT

Skin allergen testing was performed at the time of but before the lung function assessment using the previously described skin prick

method,³⁰ on the volar aspect of the forearm. The following solutions were used: 0.9% saline (negative control), 1.0 mg/ml histamine acid phosphate (positive control), whole cows' milk (1:20 w/v), egg albumen (1:20 w/v), *Dermatophagoides pteronyssinus* (dust mite) (1:50 w/v), and *Lolium perenne* (rye grass) (1:20 w/v) (Hollister-Stier, Miles Inc, Pharmaceutical Division). Skin tests were read after 15 minutes and a wheal equal to or greater than 2 mm in diameter was recorded as a positive response. All skin allergen testing was completed by two investigators (SY, JA).

CORD BLOOD TOTAL CONCENTRATIONS

Cord blood total IgE concentrations were analysed by macroprist assay.³¹ Samples were assayed in duplicate and results reported as international units (IU)/ml of serum. The lower limit of detection was 0.01 IU/ml and the interassay coefficient of variation was 16.9% (unpublished).

INFANT RESPIRATORY HEALTH

During the first year of life a weekly infant diary record was completed by the parents and included information on breast or bottle feeding, the presence of cough and/or wheeze, and the occurrence of any doctor diagnosed respiratory and/or atopic illness. At the age of 2 years the modified American Thoracic Society questionnaire²⁵ detailing the child's health over the last year was completed by the parents for the 153 families who were still contactable.

DIAGNOSING BRONCHIOLITIS

From the weekly diary records and two year follow up questionnaire, an infant was identified as having had bronchiolitis on the basis of a doctor diagnosis (community based general practitioner, private paediatrician, or hospital based paediatrician). Where available, hospital inpatient records were examined to confirm the diary report and ascertain whether per nasal aspirates had been taken to determine the presence or absence of respiratory syncytial virus. In addition, the month of diagnosis was recorded to enhance the accuracy of the diary record information.

INFANT GROUP COMPARISONS

To assess whether infants who developed bronchiolitis during the first two years of life (B-All) had characteristics which differentiated them from other infants, they were prospectively compared to the whole study population (cohort), excluding those with a diagnosis of bronchiolitis. The B-All group were subdivided into those that acquired bronchiolitis in the first (B-1) or second year (B-2) of life and were prospectively compared with each other, as well as to the cohort. Of the 10 who developed bronchiolitis in the first year, six had the episode before the 6 months' study and four between the 6 and 12 month study. None had bronchiolitis in the first two months. To

determine the incidence of respiratory symptoms during the first year of life, excluding symptoms associated with the episode of bronchiolitis, a control group of infants matched for those confounders known to be associated with lower respiratory symptoms such as age, gender, and family history of asthma, atopy, and parental smoking (matched controls) were compared with the B-1 group. The subjects were selected randomly without any knowledge of lung function measurements.

STATISTICS

Descriptive anthropometric data at each infant assessment was compared between the groups using the Student's unpaired *t* test. The Kruskal-Wallis test was used to determine if there was a difference between groups at each age for lung function measures, IgE concentrations, duration of cough and wheeze, duration of breast feeding, number of older siblings, and SaO₂ levels. Where differences were indicated, the Mann-Whitney U test was used to identify comparisons of significance. PC₄₀ levels were normalised by log transformation and between group comparisons made by parametric analysis of variance and the Student's unpaired *t* test. To determine the distribution of the bronchiolitic infants throughout the whole study population, $\dot{V}_{max}FRC$, Tme/Te, and PC₄₀ levels were divided into terciles and χ^2 and odds ratio analyses were used to compare subjects in the lower tercile with those in the upper two terciles. The χ^2 test for trend was used to compare groups for family history of asthma, atopy, and parental smoking habit, socioeconomic status, and the incidence of cough, wheeze, asthma, and eczema. Odds ratios were calculated to identify associations between family history and risk for bronchiolitis. Statistical significance was accepted if a *p* value less than 0.05 was obtained.

Results

Of the 253 infants studied during the first year of life, 17 (10 girls) reported a doctor diagnosed episode of bronchiolitis (B-All). This represented 7% of the study population. Of these 17, 10 (six girls) were diagnosed in their first year of life (B-1) and seven (four girls) in their second year (B-2). Hospital admission was required for two B-1 infants, that is, 1% of infants. Virology results were available only for those admitted to hospital and both were confirmed positive for

Table 1 Number of infants with positive family history (% of study group)

	B-All (n=17)	B-1 (n=10)	B-2 (n=7)	Cohort (n=236)
Atopy*	12 (70)	7 (70)	5 (71)	166 (71)
Asthma*	9 (53)	4 (40)	5 (71)†	93 (40)
Parents smoke (either or both)	7 (41)	4 (40)	3 (43)	116 (51)
Mother smokes	5 (29)	3 (30)	2 (29)	71 (32)

*Atopy history in primary relatives (parents and siblings).

†B-2 v cohort 0.05 < *p* < 0.10.

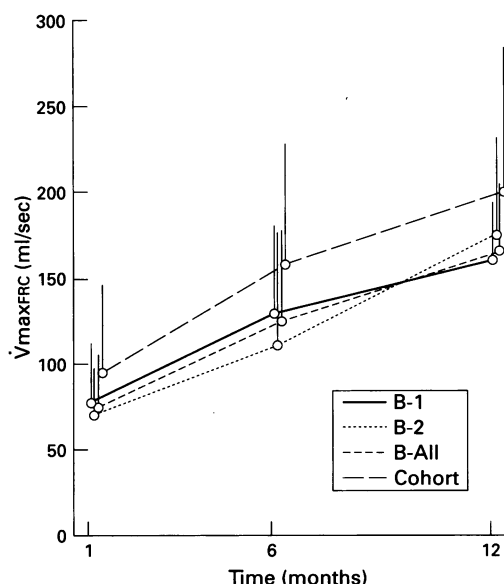


Figure 1 Mean (SE) baseline $\dot{V}_{\max FRC}$ during the first year of life.

respiratory syncytial virus. No infant with a diagnosis of bronchiolitis in the second year of life was admitted. In all but one infant, where diagnosis was made during a summer month, the reported episode occurred during the winter months between May and September in Australia, demonstrating the winter cluster pattern extensively described for bronchiolitis.³²

B-All, B-1, B-2, and the cohort were compared:

FAMILY HISTORY

A description of the family history of asthma and atopy in primary relatives and parental smoking habit during the pregnancy for infants with a report of bronchiolitis and the whole study population is presented in table 1. Seventy one per cent of the cohort had a family history of atopy, 40% a history of asthma, and

32% had mothers who smoked cigarettes. No differences were observed for the prevalence of asthma, atopy, or parental smoking between B-All and the cohort. However, a trend was present for B-2 infants to have an increased incidence of a family history of asthma in comparison to the cohort ($0.05 < p < 0.10$). This was not observed for B-1 infants.

Descriptive data showed no differences among the groups for birth weight, study age, or weight at any assessment (data not shown). At 27 weeks of age the B-All infants were shorter (mean (SD) 65.4 (3.0) cm) in comparison with the cohort 67.3 (3.0) cm ($p < 0.05$) but this difference was not present at any other age.

RESPIRATORY FUNCTION

At the age of 5 weeks, before any lower respiratory illness, B-All infants had a trend towards a reduced mean baseline lung function with mean (SE) $\dot{V}_{\max FRC}$ of 75 (8) ml/sec in comparison to the cohort with 95 (3) ml/sec ($p < 0.08$) (fig 1). Three infants had flow limitation during tidal expiration with a mean (SE) baseline $\dot{V}_{\max FRC}$ of 32 (5) ml/sec. The two infants subsequently requiring hospitalisation had baseline $\dot{V}_{\max FRC}$ values of 66 and 68 ml/sec, respectively. There was no difference in mean (SE) baseline lung function between B-1 infants and the B-2 group (78 (11) v 70 (10) ml/sec). Although mean baseline $\dot{V}_{\max FRC}$ in the bronchiolitics remained lower than the cohort at 27 and 55 weeks of age this was not statistically significant. Standardising $\dot{V}_{\max FRC}$ for length did not affect the results.

Baseline $\dot{V}_{\max FRC}$ values for the whole study population at the age of 5 weeks were ranked into terciles and the odds of subsequently developing bronchiolitis with a $\dot{V}_{\max FRC}$ in the lower tercile compared with the upper two terciles were determined. There was a trend for infants in the lower tercile at 5 weeks of age to be at increased risk of bronchiolitis during the first year of life (odds ratio 3.16, 95% confidence interval 0.87 to 11.6; $p < 0.06$), but there was no association between baseline $\dot{V}_{\max FRC}$ and bronchiolitis during the second year of life.

Assessment of passive lung mechanics of the total respiratory system during the first year of life (table 2) showed no differences between any of the infant groups at any age for either size corrected Crs or Rrs. Tme/Te and SaO_2 levels were also not different between any of the infant groups at any study age (table 3). Tercile analysis of Tme/Te at the age of 5 weeks showed no difference in tercile distribution between those that did or did not subsequently develop bronchiolitis or those that experienced bronchiolitis during the first or second year of life.

AIRWAY RESPONSIVENESS

Although mean values of PC_{40} were lower in the bronchiolitis group than the cohort at 27 weeks, there were no significant differences in

Table 2 Passive respiratory mechanics during the first year of life; mean (SE)

	B-All	B-1	B-2	Cohort
Crs (ml/cm H ₂ O/kg)				
5 Weeks	1.5 (0.1)	1.4 (0.1)	1.5 (0.2)	1.4 (0.03)
27 Weeks	1.3 (0.1)	1.2 (0.1)	1.4 (0.4)	1.3 (0.03)
55 Weeks	1.5 (0.2)	1.4 (0.1)	1.7 (0.5)	1.5 (0.04)
Rrs (cm H ₂ O (ml/sec))				
5 Weeks	0.058 (0.004)	0.060 (0.005)	0.056 (0.004)	0.056 (0.001)
27 Weeks	0.040 (0.001)	0.042 (0.002)	0.038 (0.002)	0.056 (0.002)
55 Weeks	0.034 (0.002)	0.031 (0.002)	0.042 (0.004)	0.034 (0.001)

No significant differences among study groups at any age.

Table 3 Tme/Te and SaO_2 during the first year of life

	B-All	B-1	B-2	Cohort
Mean (SE) Tme/Te				
5 Weeks	0.329 (0.029)	0.304 (0.035)	0.365 (0.050)	0.337 (0.010)
27 Weeks	0.278 (0.031)	0.298 (0.036)	0.213 (0.052)	0.271 (0.010)
55 Weeks	0.272 (0.023)	0.242 (0.012)	0.342 (0.060)	0.261 (0.010)
Median (range) SaO_2 (%)				
5 Weeks	99 (96–100)	98 (97–100)	99 (96–100)	99 (90–100)
27 Weeks	97 (90–100)	97 (90–99)	98 (93–100)	97 (89–100)
55 Weeks	97 (95–100)	96 (95–99)	98 (96–100)	97 (90–100)

No significant differences between study groups at any age.

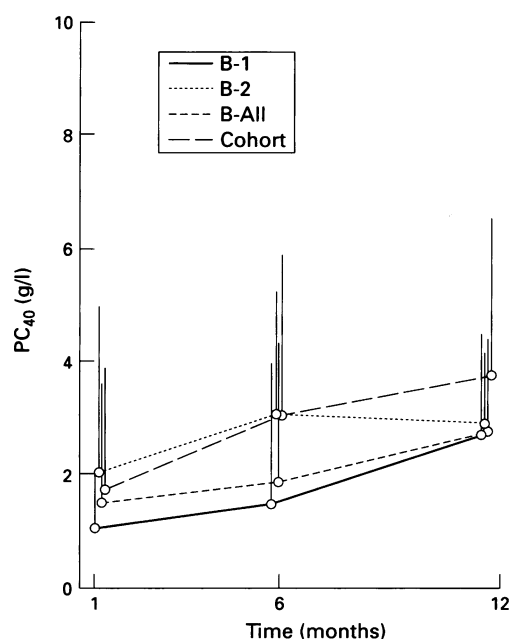


Figure 2 Geometric mean (SE) airway responsiveness to inhaled histamine during the first year of life.

the level of histamine responsiveness among the infant groups at any age (fig 2). Tercile analysis of PC_{40} values at the age of 5 weeks showed no association between tercile distribution and subsequent bronchiolitis.

CORD IgE AND SKIN ALLERGEN SENSITIVITY

No differences were found for the median cord blood IgE concentrations among any of the infant groups (table 4). The incidence of skin allergen responsiveness for each infant group is also presented in table 4. For all infant groups the peak incidence of skin test positivity occurred at the age of 27 weeks. Throughout the first year of life, cows' milk and egg white were the allergens that most frequently elicited a response in each of the infant groups, with house dust mite being the least frequent. B-All had an increased incidence of skin test positivity in comparison with the cohort ($p < 0.05$; table 4). On dividing B-All into B-1 and B-2, it was observed that the B-2 infants had an increased incidence of skin test positivity (57%) in comparison with the cohort (22%) ($p < 0.05$). B-1 infants were not different from the cohort. Incidence of skin test positivity between the B-1 and B-2 groups did not differ, although it was noted that only B-2 infants were sensitive to house dust mite.

LOWER RESPIRATORY SYMPTOMS DURING THE FIRST YEAR OF LIFE

Information detailing the duration of cough and wheeze during the episode of bronchiolitis was only available for B-1 infants due to the first year diary being a weekly record while the two year questionnaire was an overview of the child's respiratory health from age 1 to 2 years. Six of the 10 B-1 infants had a report of cough and wheeze with bronchiolitis, three reported cough only, and one wheeze only. The episode of bronchiolitis was associated with a minimum symptom duration of two weeks in all infants.

Before diagnosis, 40% of the B-1 infants had reports of wheeze during 2.5 of the weeks (range 2–16) and 60% had coughed during 9.5 of the weeks (range 1–25). Each B-1 infant was matched to a control infant for age, gender, and family history of asthma, atopy, and parental smoking to determine symptom frequency in relation to the timing of the episode of bronchiolitis. For the same time period, no matched control infant wheezed and 40% had coughed during five of the weeks (range 1–8). From the end of the episode of bronchiolitis to the end of their first year of life, 60% of the B-1 infants had wheeze reported during three of the weeks (range 1–25) and 50% coughed 12 of the weeks (range 4–17). In comparison, for the same time period, only two of the matched controls wheezed, one infant for one week only and the other for 15 of the weeks, and 40% had a record of cough during six of the weeks (range 1–21).

LOWER RESPIRATORY SYMPTOMS AND ATOPIC DISORDERS AT AGE 2 YEARS

One hundred and fifty three of the original 236 families were reviewed at two years. There was no difference in family history or initial test results between this group and the others who were unable to be followed up.

Cough was the most frequently reported symptom in the whole cohort (66%), while 42% wheezed (table 5). No differences were observed among the groups for the incidence of cough. Wheeze was reported in 42% of the cohort and 56% of the bronchiolitis. Further analysis indicated that while 100% of the B-2 infants had reports of wheeze in the second year of life (by definition), only 22% of the B-1 group reported wheeze in the second year (table 5).

An increased incidence of diagnosed asthma by the age of 2 years was observed in the B-All

Table 4 Cord IgE concentrations and infant skin allergen responses during the first year of life

	B-All	B-1	B-2	Cohort
	<i>n</i> = 11	<i>n</i> = 7	<i>n</i> = 4	<i>n</i> = 158
Median (range) IgE (IU/ml)	0.20 (0.03–0.66)	0.10 (0.03–0.66)	0.22 (0.09–0.57)	0.20 (0.01–3.4)
	<i>n</i> = 17	<i>n</i> = 10	<i>n</i> = 7	<i>n</i> = 236
No (%) with positive skin test reaction	8 (47)*	4 (40)	4 (57)*	51 (22)
Total No positive responses to all allergens	14	7	7	87
No of positive responses (% of all positive responses)				
<i>Dermatophagoides pteronyssinus</i>	2 (14)	0	2 (28)	0
<i>Lolium perenne</i>	2 (14)	1 (14)	1 (14)	16 (18)
Cows' milk	6 (43)	4 (57)	2 (28)	32 (37)
Egg white	4 (28)	2 (28)	2 (28)	39 (45)

Cord IgE: no significant differences between infant groups.

Skin reactivity: *B-All *v* cohort, $p < 0.05$; B-2 *v* cohort, $p < 0.05$.

Table 5 Incidence of lower respiratory symptoms and atopic disorders reported at the age of 2 years; number (%)

	B-All (n=16)	B-1 (n=9)	B-2 (n=7)	Cohort (n=153)
Cough	11 (69)	5 (56)	6 (86)	101 (66)
Wheeze	9 (56)	2 (22)	7 (100)†	64 (42)
Asthma	7 (44)*	2 (22)	5 (71)†	28 (18)
Eczema	7 (44)	4 (44)	3 (43)	63 (41)

Cough: no significant differences among infant groups.

Wheeze: †B-2 v cohort, $p < 0.01$.

Asthma: *B-All v cohort, $p < 0.05$; †B-2 v cohort, $p < 0.05$.

Eczema: no significant differences among infant groups.

group (44%) in comparison to the cohort (18%). Division of the B-All group showed that 71% of the B-2 infants had asthma in comparison to 22% of B-1 infants (table 5). Eczema was diagnosed in 41% of the study cohort by the age of 2 years and 44% of the bronchiolitis. No differences were observed among any of the infant groups (table 5).

Ninety per cent of the cohort were breast fed for a duration range of 2–52 weeks and 100% of the B-All group for a duration of 13–52 weeks. No differences were observed for either the proportion of infants breast fed or the duration of breast feeding among the infant groups. No differences were observed between the infant groups for number of older siblings or the socioeconomic status of the family (data not shown).

Discussion

The uniqueness of this study lies with the prospective, longitudinal documentation of respiratory function, airway responsiveness, and incidence of lower respiratory symptoms before and after an episode of bronchiolitis during the first two years of life. This is also one of only a small number of studies in the literature which is based on a community rather than a hospital based cohort. Therefore, this study more clearly describes the predisposing factors for and outcome of bronchiolitis in the general community than does a hospital based cohort which represents only those infants with the more severe form of disease who may have different predisposing characteristics and sequelae than the majority that develop bronchiolitis not requiring hospital admission. A previous study hypothesised that bronchiolitis in infancy led to lower respiratory morbidity in later childhood,³ but no physiological data on the state of the infant respiratory system before bronchiolitis had been reported, thereby preventing the testing of the proposed hypothesis. Our study would suggest that the episode of bronchiolitis is not the sole cause of subsequent respiratory morbidity as pre-existing abnormalities in lung function and frequent lower respiratory symptoms have been documented before the bronchiolitis.

Diverse diagnostic criteria have been used to define bronchiolitis. In general, hospital based studies characterise bronchiolitis as coryzal symptoms followed by rapid onset of fever, wheeze, tachypnoea, chest recession, crepitations and wheeze on auscultation, with radio-

graphic evidence of hyperinflation.^{2 6 8 10 12 13} In addition, some require a positive identification of respiratory syncytial virus by per nasal aspirate^{7 11–13} while others do not, accepting the occurrence of infection at a time when respiratory syncytial virus is prevalent in the community as indirect evidence of the probable viral causative agent.¹⁴ While some investigators diagnose bronchiolitis up to the age of 2 years,^{5 8 10} others limit the diagnosis to the first 12 months of age.³² In previously reported community based studies, the criteria for defining bronchiolitis have included a physician diagnosis and the first episode of wheezing in a child less than 2 years of age.⁵

Due to study design, the criteria used in our study to identify bronchiolitis was limited to physician diagnosis in a child under the age of 2 years. To enhance the accuracy of the reported diagnosis, the infant diaries were examined to confirm that lower respiratory symptoms were present in association with the diagnosis. Also, the month in which the diagnosis was made was noted and, in all but one infant, the episode was reported in the period of peak incidence of respiratory syncytial virus bronchiolitis documented for Australia.³² Although a diagnosis of bronchiolitis in a summer month is unusual it is not unknown,³² and therefore we did not exclude the infant from analysis. Using these criteria, 17 infants were diagnosed with bronchiolitis during the first two years of life, that is, 7% of the study population, and of these, two (1%) required hospitalisation. These figures are in concordance with the documented incidence of bronchiolitis in the literature.^{2 3 33}

One of the contentious issues regarding the definition of bronchiolitis is the age of the diagnosis – under 1 year or 2 years of age? In this study bronchiolitis was reported throughout the first two years of life; however, we were interested in whether (a) there were predisposing and/or outcome differences between infants with a diagnosis in the first or second year and (b) whether the entity labelled bronchiolitis in the second year of life was the same as that being reported in the first year. The data suggest that the episode of lower respiratory illness labelled bronchiolitis in the second year of life is more likely to be asthma. Those infants with a diagnosis of bronchiolitis in the second year of life had a particularly high genetic risk of developing asthma (71% primary family history), all wheeze, had higher rates of positive skin allergen tests, and 71% of the infants had a subsequent diagnosis of asthma. This outcome differs from those that had bronchiolitis in the first year in whom only 22% had a diagnosis of asthma at the age of 2 years. It may be possible that those infants with asthma who wheezed for the first time with a viral respiratory infection in the second year of life initially received a diagnosis of bronchiolitis.

The relative contributory roles of genetic and environmental factors to predisposing infants for bronchiolitis is another contentious issue. A number of follow up studies have identified an association between a

family history of asthma and/or atopy and an episode of bronchiolitis.^{4 5 8} Other investigators, however, have not observed this association,^{7 10-13 15 17 20 22} and in particular, a prospective longitudinal study of a group of infants believed to be at high risk for lower respiratory illness, defined by family history, observed that no infant had an episode of bronchiolitis during the first year of life.²² Our study was unable to show significant differences in family history between those that did and did not get bronchiolitis during the first year of life, however, it should be noted that our study population is biased towards those with an 'at risk' history due to the increased willingness of members of the general population with histories of asthma and allergic disease to participate in the study in comparison with those with no such histories. Of interest is that those with a diagnosis of bronchiolitis during the second year of life, had an increased family history of asthma in primary relatives.

Environmental factors suggested in previous studies as important predisposing influences for bronchiolitis include parental tobacco smoking (particularly maternal), number of older siblings, breast feeding, and socioeconomic status of the family.^{3-5 21 34} We did not observe any differences for these parameters between infants who did and did not develop bronchiolitis. This may be due to our small sample size and the lack of variation in socioeconomic status within the study population. These environmental factors do seem important agents contributing to increased severity of lower respiratory symptoms and admission to hospital. Exposure to maternal tobacco smoke has been documented to result in reduced infant lung function in this and other cohorts.^{24 35}

One of the most pressing questions arising from the literature to date is whether the lung function abnormalities documented in childhood were caused by bronchiolitis during infancy or were in fact present before the infection. Martinez and colleagues have shown that decreased pulmonary function in early life was predictive of subsequent wheeze,^{36 37} and therefore they have proposed that early life lung function predisposes certain infants for wheezing respiratory illnesses. We observed that at the age of 5 weeks, infants that were destined to develop bronchiolitis tended to have reduced respiratory function as determined by $\dot{V}_{\max FRC}$, an indicator of small airway calibre. At 6 and 12 months of age there were no differences in respiratory function between those that did and did not develop bronchiolitis.

Several authors have shown marked changes in respiratory mechanics during the acute phase of bronchiolitis with persistence of abnormality for a period of time after the acute phase.^{23 38} In this study we measured passive mechanics of the total respiratory system and found no differences in size corrected compliance and resistance before or after infection, or between those that did and did not develop bronchiolitis. If we had measured

passive mechanics during the acute phase of the infection, changes may possibly have been observed, however, our results do indicate that passive lung mechanics do not identify those predisposed for bronchiolitis or are affected adversely subsequent to the episode. This inability of Tme/Te ratio to predict those who developed bronchiolitis, as reported by Martinez *et al*,³⁷ was probably due to the small number in this cohort. Differences in oxygenation levels many years after bronchiolitis have also been described,^{10 18} however we did not observe any differences in SO_2 levels before or after bronchiolitis. These other studies were based on cohorts of infants with more severe bronchiolitis requiring hospital admission.

Several studies have shown that airway responsiveness to cold dry air,³⁹ methacholine,⁴⁰ and histamine^{24 27} is present in normal infants and that the level of airway responsiveness in early life is influenced by the family history of asthma and parental smoking.²⁴ The relationship between the level of airway responsiveness and lower respiratory illness during infancy is unclear, as evidenced in a study by Stick and colleagues where the degree of airway sensitivity in recurrently wheezy infants was found not to be different from that of normal healthy individuals.⁴¹ Many studies in the literature document an increase in airway responsiveness in infants¹⁴ and older children^{3 6 7 12 13 16 17} after bronchiolitis. Once again the dilemma that has arisen from these observations is whether increased airway sensitivity was present before the infection or was a result of infection. Although there appeared to be increased airway responsiveness at 27 weeks in those that developed bronchiolitis, our study could not demonstrate that an episode of bronchiolitis was related to or caused increased airway responsiveness. This tendency to increased responsiveness at 27 weeks which followed the episode of bronchiolitis in six infants concurs with the data available from a study in adults where airway reactivity was shown to be increased for a short period after respiratory syncytial virus infection.⁴²

Even allowing for the genetic bias in our study population, it would appear that the occurrence of lower respiratory symptoms during the first two years of life is a common phenomenon. During the first year of life 90% of the cohort reported cough and 30% wheeze. This high incidence of lower respiratory symptoms continued into the second year of life with 66% of infants experiencing cough and 42% wheeze. For all infants, cough was the predominant symptom experienced whereas wheeze was the more discriminatory symptom. Infants with an at risk family history tended to have an increased incidence of wheeze in comparison with those without such a history. Those that developed bronchiolitis reported a higher incidence of symptoms throughout the first two years of life. As with respiratory function and airway responsiveness, an association has been demonstrated between an episode of bronchiolitis and

subsequent incidence of wheeze.^{3 6-8 12 15 16 20} Our study indicates that those who develop bronchiolitis experienced an increased incidence of lower respiratory symptoms, usually of minor significance and not requiring medical attention, before the reported episode of infection. This would again suggest that bronchiolitis itself is not inducing lower respiratory symptoms in previously asymptomatic infants. From our data the bronchiolitic symptom scenario appears to be cough and wheeze before, during, and after infection.

Controversy exists as to whether an episode of bronchiolitis is the first manifestation of asthma. In our study, by the age of 2 years, those with a history of bronchiolitis had an increased incidence of asthma (44%) in comparison with the cohort (18%). However, bronchiolitis alone does not appear to be causative of asthma, as only 22% of those with a diagnosis in the first year of life had asthma by age 2 years. Seventy one per cent of infants with a diagnosis of bronchiolitis between year one and two received a diagnosis of asthma which would tend to suggest that bronchiolitis is causative; however, this group of infants had a significant genetic risk for asthma and it is more probable that the episode diagnosed as bronchiolitis in this age bracket was asthma.

In conclusion we suggest that the abnormal pulmonary function and increased incidence of lower respiratory symptoms documented in older children after an episode of bronchiolitis in infancy represents differences present from early life in these individuals. This study has demonstrated reduced pulmonary function and increased symptom incidence in infants *before* bronchiolitis. Therefore, we propose that bronchiolitis, although potentially contributory, is not the sole cause of the lower respiratory morbidity described in older children. Evidence of pre-existing lung function abnormality does not exclude bronchiolitis then causing further damage. Due to the distinct differences observed between those who get bronchiolitis during their first and second year of life, with those in the second year more likely to be part of the asthma spectrum, the diagnosis should be restricted to those under the age of 1 year.

The authors wish to thank the families involved, for their generous and long term participation, the staff of the antenatal clinical and State Health Pathology Laboratory at Osborne Park Hospital, Karen Krska for initial cord blood IgE analysis, and Peter LeSouef, Gary Geelhoed, Amanda Reese, Debbie Turner, Stephen Stick, John Henderson, and Dean Diepeveen for contributions made during the course of this study.

Supported by the National Health and Medical Research Council (Project Nos 880910 and 910160).

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Herpesvirus 7

It pays to be circumspect. In 1992 (page 500) I wrote 'Unless another one has been discovered fairly recently there are six known human herpesviruses'. What I did not know at that time was that human herpesvirus 7 (HHV-7) had been described in 1990.

Now further work in Japan (Keiko Tanaka and colleagues, *Journal of Pediatrics* 1994; **125**: 1-5) has shown that both human herpesvirus-6 (HHV-6) and HHV-7 may cause the clinical picture of roseola infantum (exanthem subitum). Seventeen children with a clinical diagnosis of roseola were studied. Two had blood taken for virus isolation and HHV-7 was isolated in both cases. In all, seven children showed seroconversion to HHV-7. Only one of these had not previously seroconverted to HHV-6. Seven patients with roseola seroconverted to HHV-6 with the illness and three patients showed no serological evidence of recent infection with either HHV-6 or HHV-7.

It seems, therefore, that roseola infantum may be caused by either HHV-6 or HHV-7 but children are usually infected with HHV-6 first. Infection with one virus does not confer immunity to the other. Some children have two episodes of roseola, the first due to HHV-6 and the second to HHV-7 but in others the second (HHV-7) infection gives rise to non-specific symptoms of upper respiratory tract infection. A few cases of roseola may be caused by other agents.

I have commented before (1992; **67**: 500) about the Japanese contribution to medicine. One hundred years ago *JAMA* (1894; **23**: 286) quoted from an editorial in an English publication, *Medical Press*, to the following effect: 'The mere fact of such a discovery (isolation of the bacillus of bubonic plague) ... is itself an eloquent testimony to the intellectual powers of a versatile and capable nation'.¹ How do I come up with such original thoughts? You may well ask.

ARCHIVIST

¹ Flanagan A, Sullivan-Fowler M. Kitasato's discovery. *JAMA* 100 years ago. *JAMA* 1994; **272**: 413.